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Request for grant of a patent

1/77

The Patent Office

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1.	Your reference	TSJ/SVH/44583GB1
2.	Patent application number	0321608.2 15 SEP 2003
3.	Full name, address and post code of the or each applicant	Vectura Ltd 1 Prospect West Chippenham Wiltshire SN14 6FH
	Patents ADP number	8607270001
	If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
4.	Title of the invention	Methods for Preparing Pharmaceutical Compositions
5.	Name of your agent	VENNER, SHIPLEY & CO
	"Address for service" in the United Kingdom to which all correspondence should be sent	20 LITTLE BRITAIN LONDON EC1A 7DH
	Patents ADP	1669004

6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and the or each application number	Country	Priority application number	Date of filing
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and filing date of the earlier application		Number of earlier application	Date of Filing

Patents Form 1/77

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'YES' if:*
a) any applicant in 3. above is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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Yes

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	39
Claim(s)	2 DL
Abstract	1
Drawing(s)	11+11

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Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents	

11. I/We request the grant of a patent on the basis of this application.

Signature: Venner, Shipley

Date: 15 September 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

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Methods for Preparing Pharmaceutical Compositions

The present invention relates to improvements in dry powder formulations comprising a pharmaceutically active agent for administration by inhalation, and in particular to methods of preparing dry powder compositions with improved properties.

The lung provides an obvious target for local administration of formulations which are intended to cure or alleviate respiratory or pulmonary diseases, such as cystic fibrosis (CF), asthma, lung cancer, etc. The lung also provides a route for delivery of systemically acting formulations to the blood stream, for example, for delivery of active agents which are not suitable for oral ingestion, such as agents that degrade in the digestive tract before they can be absorbed, like insulin.

It is well established that delivering pharmaceutically active agents to the lung by pulmonary inhalation of a dry powder has a number of advantages which make this an attractive mode of delivery.

However, the delivery of dry powder particles of pharmaceutical products to the respiratory tract presents certain problems. The inhaler device, which is preferably a bespoke device, such as a dry powder inhaler (DPI), should deliver the maximum possible proportion of the particles of pharmaceutically active agent (active particles) to the lungs. Indeed, a significant proportion of the active particles should be deposited in the lower lung, preferably even at the low inhalation capabilities to which some patients, especially asthmatics, are limited. However, when using many dry powder formulations, it has been found that frequently only a small proportion (often only about 10%) of the active particles that leave the device on actuation are actually deposited in the lower lung. As a result, much work has been done on improving dry powder formulations to enhance the delivery of the active particles to the lower respiratory tract or deep lung.

The type of dry powder inhaler used can influence the proportion of the active particles delivered to the lung, as different types of inhaler devices provide different

air flow conditions which lead to the active particles reaching the respiratory tract. Also, the physical properties of the powder affect both the efficiency and reproducibility of delivery of the active particles and the site of deposition in the respiratory tract.

On exit from the inhaler device, the active particles should form a physically and chemically stable aerocolloid which remains in suspension until it reaches a conducting bronchiole or smaller branching of the pulmonary tree or other absorption site, preferably in the lower lung. Once at the absorption site, the active particles should be capable of efficient collection by the pulmonary mucosa with no active particles being exhaled from the absorption site.

When delivering a formulation to the lung for local or systemic action, the size of the active particles within the formulation is very important in determining the site of the absorption in the body.

For formulations to reach the deep lung or the blood stream via inhalation, the active agent in the formulation must be in the form of very fine particles, for example, having a mass median aerodynamic diameter (MMAD) of less than 10μm. It is well established that particles having an MMAD of greater than 10μm are likely to impact on the walls of the throat and generally do not reach the lung. Particles having an MMAD in the region of 5 to 2μm will generally be deposited in the respiratory bronchioles whereas particles having an MMAD in the range of 3 to 0.05μm are likely to be deposited in the alveoli or be absorbed into the bloodstream.

Preferably, for delivery to the lower respiratory tract or deep lung, the MMAD of the active particles is not more than 10μm, and preferably not more than 5μm, more preferably not more than 3μm, and may be less than 1μm. Ideally, at least 90% by weight of the active particles in a dry powder formulation should have an MMAD of not more than 10μm, preferably not more than 5μm, more preferably not more than 3μm, and most preferably not more than 1μm.

When dry powders are produced using conventional processes, the active particles will vary in size, and often this variation can be considerable. This can make it difficult to ensure that a high enough proportion of the active particles are of the appropriate size for administration to the correct site. It is therefore desirable to have a dry powder formulation wherein the size distribution of the active particles is as narrow as possible. This will improve dose efficiency and reproducibility.

Fine particles, that is, those with an MMAD of less than 10μm and smaller tend to be increasingly thermodynamically unstable as their surface area to volume ratio increases, which provides an increasing surface free energy with this decreasing particle size, and consequently increases the tendency of particles to agglomerate and the strength of the agglomerate. In the inhaler, agglomeration of fine particles and adherence of such particles to the walls of the inhaler are problems that result in the fine particles leaving the inhaler as large, stable agglomerates, or being unable to leave the inhaler and remaining adhered to the interior of the inhaler, or even clogging or blocking the inhaler.

The uncertainty as to the extent of formation of stable agglomerates of the particles between each actuation of the inhaler, and also between different inhalers and different batches of particles, leads to poor dose reproducibility. Furthermore, the formation of agglomerates means that the MMAD of the active particles can be vastly increased, with agglomerates of the active particles not reaching the required part of the lung.

The metered dose (MD) of a dry powder formulation is the total mass of active agent present in the metered form presented by the inhaler device in question. For example, the MD might be the mass of active agent present in a capsule for a Cyclohaler (trademark), or in a foil blister in an Aspirair (trademark) device.

The emitted dose (ED) is the total mass of the active agent emitted from the device following actuation. It does not include the material left on the internal or external surfaces of the device, or in the metering system including, for example, the capsule or blister. The ED is measured by collecting the total emitted mass from the device

in an apparatus frequently identified as a dose uniformity sampling apparatus (DUSA), and recovering this by a validated quantitative wet chemical assay.

The fine particle dose (FPD) is the total mass of active agent which is emitted from the device following actuation which is present in an aerodynamic particle size smaller than a defined limit. This limit is generally taken to be 5μm if not expressly stated to be an alternative limit, such as 3μm, 2μm or 1μm, etc. The FPD is measured using an impactor or impinger, such as a twin stage impinger (TSI), multi-stage impinger (MSI), Andersen Cascade Impactor or a Next Generation Impactor (NGI). Each impactor or impinger has a pre-determined aerodynamic particle size collection cut points for each stage. The FPD value is obtained by interpretation of the stage-by-stage active agent recovery quantified by a validated quantitative wet chemical assay where either a simple stage cut is used to determine FPD or a more complex mathematical interpolation of the stage-by-stage deposition is used.

The fine particle fraction (FPF) is normally defined as the FPD divided by the ED and expressed as a percentage. Herein, the FPF of ED is referred to as FPF(ED) and is calculated as FPF(ED) = (FPD/ED) x 100%.

The fine particle fraction (FPF) may also be defined as the FPD divided by the MD and expressed as a percentage. Herein, the FPF of MD is referred to as FPF(MD), and is calculated as FPF(MD) = (FPD/MD) x 100%.

The tendency of fine particles to agglomerate means that the FPF of a given dose is highly unpredictable and a variable proportion of the fine particles will be administered to the lung, or to the correct part of the lung, as a result.

In an attempt to improve this situation and to provide a consistent FPF and FPD, dry powder formulations often include additive material.

The additive material is intended to decrease the cohesion between particles in the dry powder formulation. It is thought that the additive material interferes with the weak bonding forces between the small particles, helping to keep the particles

separated and reducing the adhesion of such particles to one another, to other particles in the formulation if present and to the internal surfaces of the inhaler device. Where agglomerates of particles are formed, the addition of particles of additive material decreases the stability of those agglomerates so that they are more likely to break up in the turbulent air stream created on actuation of the inhaler device, whereupon the particles are expelled from the device and inhaled. As the agglomerates break up, the active particles return to the form of small individual particles which are capable of reaching the lower lung.

In the prior art, dry powder formulations are discussed which include distinct particles of additive material (generally of a size comparable to that of the fine active particles). In some embodiments, the additive material may form a coating, generally a discontinuous coating, on the active particles and/or any carrier particles.

Preferably, the additive material is an anti-adherent material and it will tend to reduce the cohesion between particles and will also prevent fine particles becoming attached to the inner surfaces of the inhaler device. Advantageously, the additive material is an anti-friction agent or glidant and will give better flow of the pharmaceutical composition in the inhaler. The additive materials used in this way may not necessarily be usually referred to as anti-adherents or anti-friction agents, but they will have the effect of decreasing the cohesion between the particles or improving the flow of the powder. The additive materials are often referred to as force control agents (FCAs) and they usually lead to better dose reproducibility and higher fine particle fractions.

Therefore, an FCA, as used herein, is an agent whose presence on the surface of a particle can modify the adhesive and cohesive surface forces experienced by that particle, in the presence of other particles. In general, its function is to reduce both the adhesive and cohesive forces.

In general, the optimum amount of additive material to be included in a dry powder formulation will depend on the chemical composition and other properties of the

additive material and of the active material, as well as upon the nature of other particles such as carrier particles, if present. In general, the efficacy of the additive material is measured in terms of the fine particle fraction of the composition.

Known additive materials usually consist of physiologically acceptable material, although the additive material may not always reach the lung. For example, where the additive particles are attached to the surface of carrier particles, they will generally be deposited, along with those carrier particles, at the back of the throat of the user.

Preferred additive materials used in the prior art dry powder formulations include amino acids, peptides and polypeptides having a molecular weight of between 0.25 and 1000 kDa and derivatives thereof, dipolar ions such as zwitterions, phospholipids such as lecithin, and metal stearates such as magnesium stearate.

In a further attempt to improve this situation and to provide a consistent FPF and FPD, dry powder formulations often include coarse carrier particles of excipient material mixed with fine particles of active material. Rather that sticking to one another, the fine active particles tend to adhere to the surfaces of the coarse carrier particles whilst in the inhaler device, but are supposed to release and become dispersed upon actuation of the dispensing device and inhalation into the respiratory tract, to give a fine suspension. The carrier particles preferably have MMADs greater than 90μm.

The inclusion of coarse carrier particles is also very attractive where very small doses of active agent are dispensed. It is very difficult to accurately and reproducibly dispense very small quantities of powder and small variations in the amount of powder dispensed will mean large variations in the dose of active agent where the powder comprises mainly active particles. Therefore, the addition of a diluent, in the form of large excipient particles will make dosing more reproducible and accurate.

Carrier particles may be of any acceptable excipient material or combination of materials. For example, the carrier particles may be composed of one or more materials selected from sugar alcohols, polyols and crystalline sugars. Other suitable carriers include inorganic salts such as sodium chloride and calcium carbonate, organic salts such as sodium lactate and other organic compounds such as polysaccharides and oligosaccharides. Advantageously, the carrier particles are of a polyol. In particular, the carrier particles may be particles of crystalline sugar, for example mannitol, dextrose or lactose. Preferably, the carrier particles are of lactose.

Advantageously, substantially all (by weight) of the carrier particles have a diameter which lies between 20μm and 1000μm, more preferably 50μm and 1000μm. Preferably, the diameter of substantially all (by weight) of the carrier particles is less than 355μm and lies between 20μm and 250μm.

Preferably at least 90% by weight of the carrier particles have a diameter between from 60μm to 180μm. The relatively large diameter of the carrier particles improves the opportunity for other, smaller particles to become attached to the surfaces of the carrier particles and to provide good flow and entrainment characteristics and improved release of the active particles in the airways to increase deposition of the active particles in the lower lung.

The ratios in which the carrier particles (if present) and composite active particles are mixed will, of course, depend on the type of inhaler device used, the type of active particles used and the required dose. The carrier particles may be present in an amount of at least 50%, more preferably 70%, advantageously 90% and most preferably 95% based on the combined weight of the composite active particles and the carrier particles.

However, a further difficulty is encountered when adding coarse carrier particles to a composition of fine active particles and that difficulty is ensuring that the fine particles detach from the surface of the large particles upon actuation of the delivery device.

The step of dispersing the active particles from other active particles and from carrier particles, if present, to form an aerosol of fine active particles for inhalation is significant in determining the proportion of the dose of active material which reaches the desired site of absorption in the lungs. In order to improve the efficiency of that dispersal it is known to include in the composition additive materials, including FCAs of the nature discussed above. Compositions comprising fine active particles and additive materials are disclosed in WO 97/03649 and WO 96/23485.

In light of the foregoing problems associated with known dry powder formulations, even when including additive material and/or carrier particles, it is an aim of the present invention to provide dry powder compositions which have physical and chemical properties which lead to an enhanced FPF and FPD. This leads to greater dosing efficiency, with a greater proportion of the dispensed active agent reaching the desired part of the lung for achieving the required therapeutic effect.

In particular, the present invention seeks to optimise the preparation of particles of active agent used in the dry powder composition by engineering the particles making up the dry powder composition and, in particular, by engineering the particles of active agent. It is proposed to do this by adjusting and adapting the spray drying process used to form the particles of active agent.

Firstly, the spray drying process may involve co-spray drying the active agent with one or more force control agents.

Secondly, the formation of the droplets in the spray drying process may be controlled, so that droplets of a given size and of a narrow size distribution may be formed. Furthermore, controlling the formation of the droplets can allow control of the air flow around the droplets which, in turn, can be used to control the drying of the droplets and, in particular, the rate of drying. Controlling the formation of the droplets may be achieved by using alternatives to the conventional 2-fluid nozzles.

Thirdly, the spray drying process may include a further step wherein the moisture content of the spray dried particles is adjusted to allow fine-tuning of some of the properties of the particles.

Whilst the FPF and FPD of a dry powder formulation are dependent on the nature of the powder itself, these values are also influenced by the type of inhaler used to dispense the powder. For example, the FPF obtained using a passive device will tend not to be as good as that obtained with the same powder but using an active device, such as an Aspirair (trade mark) device (see WO 01/00262 and GB 2 353 222).

It is an aim of the present invention to optimise the powder properties, so that the FPF and FPD are improved compared to those obtained using known powder formulations, regardless of the type of device used to dispense the composition of the invention.

It is a particular aim of the present invention to provide a dry powder formulation which has an FPF of at least 50%. Preferably, the FPF(ED) will be between 70 and 99%, more preferably between 80 and 99%. Furthermore, it is desirable for the FPD to be at least 50%. Preferably, the FPD will be between 50 and 99%, more preferably between 60 and 99%.

The present invention is described below in detail, with reference to the following drawings.

Figure 1 shows a schematic set-up of a 2-fluid nozzle spray drier.

Figures 2a-2d are SEM micrographs of 2-fluid nozzle spray dried powders which were co-spray dried with increasing amounts of l-leucine (0%, 5%, 25% and 50% w/w), without secondary drying.

Figures 2e-2h are SEM micrographs of 2-fluid nozzle spray dried powders which were co-spray dried with increasing amounts of l-leucine (2%, 5%, 10% and 50% w/w), after secondary drying.

Figure 3 shows a schematic diagram of an ultrasonic nebuliser producing fine droplet.

Figure 4 shows a schematic set-up of a spray drier incorporating an ultrasonic nebuliser.

Figures 5a and 5b show SEM micrographs of spray dried nebulised heparin alone and with 10% w/w leucine, without secondary drying.

Figure 6 shows a typical size distribution curve of three repeated tests of spray dried nebulised heparin (with no FCA).

Figures 7a-7c show a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin and leucine (2% w/w, 5% w/w and 10% w/w).

Figure 8 shows a comparison between particle size distribution curves of secondary dried and not secondary dried powders. The powder used was heparin with leucine (10% w/w).

Co-Spray Drying the Active Agent and a Force Control Agent

It has been discovered that the FPF and the FPD of a dry powder formulation may be greatly increased by co-spray drying the active agent with a force control agent.

Thus, according to a first aspect of the present invention, a method of making a dry powder composition for pulmonary inhalation is provided, the method comprising spray drying a pharmaceutically active agent to form active particles, wherein the active agent is co-spray dried with a force control agent (FCA).

In one embodiment of the invention, the dry powder compositions comprising such co-spray dried active particles exhibit a fine particle fraction (<5μm) of at least 50%. Preferably, the FPF(ED) will be between 70 and 99%, more preferably between 80 and 99%. Furthermore, it is desirable for the FPF (MD) to be at least 50%. Preferably, the FPD will be between 50 and 99%, more preferably between 60 and 99%.

The combination or blend of active agent and FCA which is spray dried to form a dry powder formulation can be a solution or suspension in a host liquid. In embodiments, all or at least a proportion of the active agent and/or FCA is or are in solution in the host liquid before being subjected to spray drying. Substantially all of the active agent and FCA can be in solution in the host liquid before being subjected to spray drying.

The active agent is preferably at least 1.5, 2, 4 and, more preferably, at least 10 times more soluble than the FCA in the host liquid at the spraying temperature and pressure. In preferred embodiments, this relationship exists at a temperature between 30 and 60°C and atmospheric pressure. In other embodiments, this relationship exists at a temperature between 20 to 30°C and atmospheric pressure, or, preferably, at 20°C and atmospheric pressure.

Preferably, the FCAs used in the present invention are film-forming agents, fatty acids and their derivatives, lipids and lipid-like materials, and surfactants, especially solid surfactants.

Advantageously, the FCA includes one or more compounds selected from amino acids and derivatives thereof, and peptides and derivatives thereof. Amino acids, peptides and derivatives of peptides are physiologically acceptable and give acceptable release of the active particles on inhalation.

It is particularly advantageous for the FCA to comprise an amino acid. The FCA may comprise one or more of any of the following amino acids: leucine, isoleucine, lysine, cysteine, valine, methionine, and phenylalanine. The FCA may be a salt or a

derivative of an amino acid, for example aspartame or acesulfame K. Preferably, the FCA consists substantially of an amino acid, more preferably of leucine, advantageously L-leucine. The D-and DL-forms may also be used. As indicated above, L-leucine has been found to give particularly efficient dispersal of the active particles on inhalation.

The FCA may include one or more water soluble substances. This helps absorption of the substance by the body if the FCA reaches the lower lung. The FCA may include dipolar ions, which may be zwitterions.

Alternatively, the FCA may comprise a phospholipid or a derivative thereof. Lecithin has been found to be a good material for use as an FCA.

The FCA may comprise a metal stearate, or a derivative thereof, for example, sodium stearyl fumarate or sodium stearyl lactylate. Advantageously, the FCA comprises a metal stearate. For example, zinc stearate, magnesium stearate, calcium stearate, sodium stearate or lithium stearate. Preferably, the FCA comprises magnesium stearate.

The FCA may include or consist of one or more surface active materials, in particular materials that are surface active in the solid state. These may be water soluble or able to form a suspension in water, for example lecithin, in particular soya lecithin, or substantially water insoluble, for example solid state fatty acids such as oleic acid, lauric acid, palmitic acid, stearic acid, erucic acid, behenic acid, or derivatives (such as esters and salts) thereof, such as glyceryl behenate. Specific examples of such materials are: phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylinositol and other examples of natural and synthetic lung surfactants; lauric acid and its salts, for example, sodium lauryl sulphate, magnesium lauryl sulphate; triglycerides such as Dynsan 118 and Cutina HR; and sugar esters in general. Alternatively, the FCA may be cholesterol or natural cell membrane materials, including pollen or spore cell wall components such as sporo-pollenins.

Other possible FCAs include sodium benzoate, hydrogenated oils which are solid at room temperature, talc, titanium dioxide, aluminium dioxide, silicon dioxide and starch.

In embodiments, a plurality of different FCAs can be used.

The host liquid is preferably water, although it can be a solution of an organic co-solvent, or plurality of organic co-solvents, and water; the latter being especially useful with active agents and FCAs that are insoluble or substantially insoluble in water alone. Preferred organic co-solvents include methanol, ethanol, propan-1-ol, propan1-2-ol and acetone; with ethanol being the most preferred.

Spray drying is a well-known and widely used technique for producing particles of material. To briefly summarise, the material to be made into particles is dissolved or dispersed in a liquid or can be made into a liquid which is sprayed through a nozzle under pressure to produce a mist or stream of fine droplets. These fine droplets are usually exposed to heat which evaporates the moisture in the droplets almost instantaneously, leaving dry powder particles.

Spray drying is a widely used technique and many types of spray drying apparatus are known. The process is relatively cheap and simple. A standard method for producing particles of an active material involves using a conventional spray dryer, such as a Büchi B-191 under a "standard" set of parameters. Such standard parameters are set out in Table 1.

Table 1: "Standard" parameters used in spray drying using the Büchi B-191 spray dryer (Büchi two fluid nozzle, internal setting, 0.7mm mixing needle and cap, 100% aspirator setting).

Atomisation pressure	Inlet temp	Outlet temp	Total solid conc'n (% w/w) in solvent	Solvent (host liquid)	Feed rate (ml/min)
5 - 6 bar	150°C	~100°C	1	Aqueous	5

It has been discovered that it is possible to enhance the FPF of a dry powder composition by co-spray drying the active agent with one or more force control agents (FCAs) and/or excipients in the spray drying feedstock.

The particles produced in this way will comprise both the active agent and the FCA and so the FCA will actually be administered to the lower respiratory tract or deep lung upon inhalation of the dry powder composition. This is in contrast to the additive material used in the prior art, which often was not administered to the deep lung, for example because it remains attached to the large carrier particles.

Thus, it is important that the selected FCA does not have a detrimental effect when administered to the lower respiratory tract or deep lung. Amino acids such as leucine, lysine and cysteine are all harmless in this regard, as are other FCAs such as phospholipids and magnesium stearate, when present in small quantities.

The effects of co-spray drying an active agent and a FCA are illustrated in the following discussion of various experiments and the results obtained. In the experiments, the active agent used is heparin. The reason for selecting this active agent to illustrate and test the present invention is that heparin is a "sticky" compound and this tends to have a detrimental effect on the FPF and FPD of the dry powder. Therefore, obtaining good values of FPF and FPD using heparin is an indication that the compositions really do exhibit good and improved properties, regardless of the "difficult" nature of the active agent included.

The preferred active agents include:

1) steroid drugs such as, for example, alcometasone, beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, clobetasol, deflazacort, diflucortolone, desoxymethasone, dexamethasone, fludrocortisone, flunisolide, fluocinolone, fluometholone, fluticasone, fluticasone proprionate, hydrocortisone, triamcinolone, nandrolone decanoate, neomycin sulphate, rimexolone, methylprednisolone and prednisolone;

2) antibiotic and antibacterial agents such as, for example, metronidazole, sulphadiazine, triclosan, neomycin, amoxicillin, amphotericin, clindamycin, aclarubicin, dactinomycin, nystatin, mupirocin and chlorhexidine;

3) systemically active drugs such as, for example, isosorbide dinitrate, isosorbide mononitrate, apomorphine and nicotine;

4) antihistamines such as, for example, azelastine, chlorpheniramine, astemizole, cetirizine, cinnarizine, desloratadine, loratadine, hydroxyzine, diphenhydramine, fexofenadine, ketotifen, promethazine, trimeprazine and terfenadine;

5) anti-inflammatory agents such as, for example, piroxicam, nedocromil, benzydamine, diclofenac sodium, ketoprofen, ibuprofen, heparinoid, nedocromil, cromoglycate, fasafungine and iodoxamide;

6) anticholinergic agents such as, for example, atropine, benzatropine, biperiden, cyclopentolate, oxybutinin, orphenadine hydrochloride, glycopyrronium, glycopyrrolate, procyclidine, propantheline, propiverine, tiotropium, tropicamide, trospium, ipratropium bromide and oxitroprium bromide;

7) anti-emetics such as, for example, bestahistine, dolasetron, nabilone, prochlorperazine, ondansetron, trifluoperazine, tropisetron, domperidone, hyoscine, cinnarizine, metoclopramide, cyclizine, dimenhydrinate and promethazine;

8) hormonal drugs such as, for example, protirelin, thyroxine, salcotonin, somatropin, tetracosactide, vasopressin or desmopressin;

9) bronchodilators, such as salbutamol, fenoterol and salmeterol;

10) sympathomimetic drugs, such as adrenaline, noradrenaline, dexamfetamine, dipirefin, dobutamine, dopexamine, phenylephrine, isoprenaline, dopamine, pseudoephedrine, tramazoline and xylometazoline;

11) anti-fungal drugs such as, for example, amphotericin, caspofungin, clotrimazole, econazole nitrate, fluconazole, ketoconazole, nystatin, itraconazole, terbinafine, voriconazole and miconazole;

12) local anaesthetics such as, for example, amethocaine, bupivacaine, hydrocortisone, methylprednisolone, prilocaine, proxymetacaine, ropivacaine, tyrothricin, benzocaine and lignocaine;

13) opiates, preferably for pain management, such as, for example, buprenorphine, dextromoramide, diamorphine, codeine phosphate, dextropropoxyphene, dihydrocodeine, papaveretum, pholcodeine, loperamide, fentanyl, methadone, morphine, oxycodone, phenazocine, pethidine and combinations thereof with an anti-emetic;

14) analgesics and drugs for treating migraine such as clonidine, codine, coproxamol, dextropropoxypene, ergotamine, sumatriptan, tramadol and non-steroidal anti-inflammatory drugs;

15) narcotic agonists and opiate antidotes such as naloxone, and pentazocine;

16) phosphodiesterase type 5 inhibitors, such as sildenafil (viagra); and

17) pharmaceutically acceptable salts of any of the foregoing.

In preferred embodiments, the active agent is heparin, apomorphine, glycopyrrolate, or clobozam.

Preferably, the active agent is a small molecule, as opposed to a macromolecule. Preferably, the active agent is not a protein, and more preferably, the active agent is not insulin.

The active agent, preferably, exhibits greater than 20, 25, 30, and, more preferably, 40% bio-availability when administered via the lung in the absence of a penetration enhancer. Tests suitable for determining bio-availability are well known to those skilled in the art and an example is described in WO 95/00127. Agents that exhibit bio-availability of less than 20%, such as a majority of macromolecules, are

insufficiently rapidly cleared from the deep lung and, as a result, accumulate to an unacceptable extent if administered to this location on a long term basis.

A plurality of active agents can be employed in the practice of the present invention.

Unless otherwise indicated, the FPF and FDP figures given in the following sections of this specification were obtained by firing capsules, filled with approximately 20 mg of material, from a Monohaler into a multi stage liquid impinger (MSLI), at a flow rate of 90 lpm, or a twin stage or rapid twin stage impinger (TSI or rTSI) at 60 lpm. The "delivered dose" or "DD", which is referred to in some of the following sections, is the same as the emitted dose or ED (as defined above).

In order to illustrate how the present invention works, firstly the effect of adjusting the solid concentration of active agent was investigated. The active agent was spray dried (without an FCA) using the standard parameters as shown in Table 1, but the solid concentration of active agent was increased from 1% w/w to 2 and 5% w/w total solids. The effects of these changes on the FPFs were then investigated and the results were as follows.

Table 2: FPF (%) less than 5μm of the delivered dose (DD) for spray dried heparin using "standard" spray drying parameters

Description	Test	FPF <5μm (DD) (%)
1% w/w heparin	MSLI	17.0
1% w/w heparin	TSI	20.3

The FPF for heparin spray dried alone, that is, without a co-spray dried FCA, using the "standard" spray drying parameters (see Table 1) was 17-20% as shown in Table 2. Testing was done with both a multi stage liquid impinger (MSLI) and a twin stage impinger (TSI).

Table 3: FPF (%) less than 5μm of DD for heparin spray dried from increasing solid concentrations

Description	Test	FPF <5μm (DD) (%)
2% w/w heparin	rTSI	21.3
5% w/w heparin	rTSI	8.3

Increasing the solid concentration of heparin from 1% w/w (Table 2) to 5% w/w (Table 3) caused a large reduction in FPF of heparin from approximately 20% FPF to 8.3%, when tested using a rapid-TSI. 2% w/w solid content did not seem to have an effect on FPF.

Thus, increasing the solid content of the feed solution did not improve the FPF of the active particles. Increasing the solid content as high as 5% w/w reduced the FPF by more than 10%. Increasing the solid content of a feedstock without changing any of the other parameters generally causes an increase in particle size, as each droplet will have a greater mass of solid which needs to dry in the same amount of time.

Accordingly, although a solid content of up to 10 % w/w active agent, and in some cases as much as 25% w/w active agent, can be used, it is preferred for up 5%w/w, and more preferably 2 % w/w active agent to be used in the spray drying process of the present invention. It is also preferred for at least 0.05, more preferably 0.5 % w/w to be employed.

Next, the effect of spray drying an active agent with various organic solvents was evaluated. The "standard" parameters as outlined in Table 1 were used to spray dry heparin, with the only difference being that the heparin was spray dried from 10% w/w organic solvent (propan-1-ol, methanol or ethanol) in water. The results are set out in Table 4.

Table 4: FPF (%) less than 5μm of DD for heparin spray dried from an organic solvent.

Spray drying feedstock % w/w heparin	Solvent % w/w	Test	FPF <5μm (DD) (%)
1	10 % methanol	MSLI	2.3
1	10% ethanol	MSLI	6.2
1	10% propan-1-ol	MSLI	2.0

Spray drying 1% w/w heparin from 10% methanol, ethanol and propan-1-ol resulted in a lowering of FFP (Table 4) from approximately 20% when spray dried from aqueous solvent using identical parameters (Table 2) to 2-6% FPF.

One might expect that adding an organic solvent to the feedstock would cause an increase of the FPF, as a result of a reduction in the viscosity of the feedstock, and a lower energy input being required to generate smaller particles. However, the results obtained from 2-fluid nozzle spray drying of heparin from feedstocks containing 10% organic solvent (Table 4) show a reduction in FPF.

As a further test, an active agent was spray dried using the standard parameters used above (Table 1), but the effect of temperature on the particles produced was investigated by spray drying with inlet temperatures of 75°C to 220°C. The results are set out in Table 5.

Table 5: FPF (%) less than 5μm of DD for heparin spray dried using different inlet temperatures.

Inlet temperature	Approx. outlet temperature	Test	FPF <5μm (DD) (%)
220°C	135°C	MSLI	17.5
75°C	35°C	rTSI	22.5

Thus, it can be seen that spray drying heparin at a higher or lower inlet temperature relative to the "standard" 150°C normally used did not offer a substantial improvement in FPF.

A preferable range for the inlet temperature is 40°C to 300°C, preferably 75°C to 220°C. A preferable range for the outlet temperature is 20°C to 200°C, preferably 35°C to 135°C.

The effects of co-spray drying an active agent with varying amounts of the l-leucine, a FCA, from aqueous solution were then studied. Standard Büchi spray drying parameters were used, as shown in Table 1. L-leucine was included in the solution of heparin such that the percentage of l-leucine ranged from 2-50% w/w. The results are set out in Table 6.

Table 6: FPF (%) less than 5μm of DD for heparin co-spray dried with l-leucine.

Spray drying feedstock % w/w heparin	Co-spray drying with l-leucine % w/w	Test	FPF <5μm (DD) (%)
1	2%	rTSI	20.0
1	5%	MSLI	32.8
1	10%	MSLI	30.8
1	25%	MSLI	35.4
1	50%	MSLI	51.7

The results show that increasing the percentage of l-leucine included in the feedstock for spray drying resulted in a steady improvement in FPF from approximately 20% FPF with 2% leucine, to 50% FPF with 50% leucine (Table 6).

Next, 1% total solids solution was sprayed from a 2-fluid nozzle into a Büchi spray drier. Blends of heparin and l-leucine were prepared at different weight percentages of l-leucine. Powders of 2%, 5%, 10%, 25% and 50% w/w l-leucine were prepared. The spray drier feed flow rate was 120 ml/hr, the inlet temperature was 150°C, and flush nozzle setting was used. The schematic set-up of the two-fluid nozzle spray drier is shown in Figure 1.

In a first MSLI study, an internal nozzle alignment was used and the powder was not subjected to a secondary drying process. The feed rate used was 300 ml/hr.

20 mg of powder was dispersed in each case and the results set out in Table 7 indicate an improvement of FPF with addition of a FCA, although the FPD does not improve with the addition of more than 10% l-leucine due to the relative reduction of the heparin content.

Table 7: MSLI study of co-spray dried heparin and varying concentrations of leucine

Formulation	Test	ED (mg)	FPF% (emitted dose)	FPD (mg)
Heparin (0% leucine)	MSLI	10	17	1.8
Heparin + leucine (5% w/w)	MSLI	11	33	3.6
Heparin + leucine (10% w/w)	MSLI	13	31	3.9
Heparin + leucine (25% w/w)	MSLI	10	35	3.7
Heparin + leucine (50% w/w)	MSLI	6	52	3.0

Thus, in preferred embodiments, the active agent is spray dried with from 0.1 to 50% w/w FCA to active agent, preferably from 1 to 10% w/w FCA to active agent, and more preferably less than 5% w/w FCA to active agent. An added advantage of employing the preferred amounts of FCA is that the risk of toxicity problems is reduced.

In further preferred embodiments, the FCA is an amino acid, and more preferably the FCA is one or more of leucine, preferably l-leucine, isoleucine, lysine and cysteine. Most preferably, the active agent is co-spray dried with l-leucine.

It has been found that co-spray drying an active agent with an FCA, and in particular with l-leucine, isoleucine, lysine and cysteine, leads to significant changes in the particle cohesion, greatly enhancing the properties of the dry powder when administered by pulmonary inhalation. It has also been discovered that the changes to the FPF and FPD are, to an extent, dependent upon the amount of FCA being co-spray dried.

Where the spray drying takes place under "standard" parameters and using conventional spray drying apparatus, it has been found that spray drying an active agent with an FCA can lead to unusual particle morphology. At low concentrations of FCA, the surfaces of the particles show dimples or depressions. As the amount of co-spray dried FCA is increased, these dimples become more extreme, with the particles eventually having a shrivelled or wrinkled surface.

The morphology of the particles was viewed using scanning electron micrographs (SEMs). A sample preparation for this is set out below.

Pieces of double-sided carbon tape were placed on a numbered planchette. The backing was removed and small amounts of samples placed on them (the pieces of carbon tape were identified for different samples where appropriate). The backing was pressed on to ensure firm adherence of the sample to the tape. Excess sample was tapped off. Samples were coated in an Edwards Sputter Coater S150B at HT voltage 7 for an appropriate length of time (approximately 12 minutes).

SEM details: Jeol 6310. 10kV accelerating voltage. Spot size 13. Working distance 15. Noise reduction 20.

SEM micrographs of 2-fluid nozzle spray dried powders (Figures 2a-d) illustrate a clear relationship between the increasing percentage of l-leucine and an increasingly dimpled or wrinkled surface of the particles. The particles with the highest l-leucine content appear to be extremely wrinkled and, in selected cases, are possibly burst as an extreme result of "blowing", a phenomenon whereby the particles form a shell or skin which inflates and then collapses.

Droplets from the two fluid nozzle are initially dried at a relatively high rate during spray drying and this creates a viscous layer of material around the exterior of the liquid droplet. As the drying continues, the viscous layer is firstly stretched (like a balloon) by the increased vapour pressure inside the viscous layer as the solvent evaporates. The solvent vapour diffuses through the growing viscous layer until it is exhausted and the viscous layer then collapses, resulting in the formation of craters

in the surface or wrinkling of the particles. The viscosity of the viscous layer has been related to the glass transition temperature of the material by the WLF (Williams, Landel, Ferry) Equation (see Alexander et al, Drying Technology; Vol. 3, No. 3, 1985).

Figure 2a is an SEM micrograph of 2-fluid nozzle spray dried heparin (without secondary drying). The particles are generally spherical in shape and the surfaces are substantially smooth. However, the particles each have one (smooth) crater or dimple in their surface.

Figure 2b is an SEM micrograph of 2-fluid nozzle spray dried heparin with 5% leucine (without secondary drying). The particles now exhibit more dimples or craters on their surface. The particles still have a generally smooth surface.

Figure 2c is an SEM micrograph of 2-fluid nozzle spray dried heparin with 25% leucine (without secondary drying). With the increase in FCA, the surface of the particles no longer appears smooth and the generally spherical shape has disappeared. The particles have a shrivelled, deflated appearance.

Figure 2d is an SEM micrograph of 2-fluid nozzle spray dried heparin with 50% leucine (without secondary drying). The shrivelling observed in the particles of Figure 2c has become more pronounced and the particles appear to have completely collapsed, looking like empty skins or shells.

This change in the surface morphology of these co-spray dried particles appears to reduce the cohesion between the particles. Conventional particles of active material are generally spherical in shape, as seen in Figure 2a. This relatively smooth, regular shape of the fine particles means that they are likely to agglomerate, as discussed above. However, less agglomeration is observed as the irregularity of the surface of the co-spray dried particles increases. This suggests that the dimpled or wrinkled surfaces provide less surface area for attraction between the fine particles. It is also speculated that this particle morphology may even help the particles to fly when they are expelled for the inhaler device. This, together with the reduced

agglomeration, means that more of the active particles are capable of reaching the lower respiratory tract or deep lung.

Next, the effect of spray drying an active agent with various excipients was investigated. Standard spray drying parameters as shown in Table 1 were used and the various excipients tested were lactose, dextrose, mannitol and human serum albumin (HSA). The excipients were co-spray dried with heparin from aqueous solution. Between 5-50% w/w of the excipients were included, with total solid content not exceeding 1% w/w of the solution.

Table 9: FPF (%) less than 5μm of DD for heparin co-spray dried with excipients.

Spray drying feedstock % w/w	Co-spray drying excipient % w/w	Test	FPF <5μm (DD) (%)
1	5% lactose	rTSI	7.0
1	20% lactose	rTSI	5.3
1	50% lactose	rTSI	10.3
1	5% dextrose	rTSI	11.0
1	50% dextrose	rTSI	1.7
1	5% mannitol	rTSI	14.0
1	20% mannitol	rTSI	11.3
1	5% HSA	rTSI	34.0
1	50% HSA	rTSI	28.0

Inclusion of lactose (5-50%); dextrose (5-50%) and mannitol (5-20%) did not improve FPF (Table 9). In fact, for all of these excipients, FPFs fell to below the "standard" 20% for spray drying heparin. However, inclusion of 5% HSA gave an improvement of approximately 15%.

As the presence of the HSA in the active particle clearly reduces the particle cohesion, thereby increasing the FPF, HSA is considered, for the purpose of the present invention, to be a FCA. However, in another embodiment of the invention, the FCA is not HSA.

According to another embodiment of the present invention, the active agent is co-spray dried with HSA. Preferably, the active agent is co-spray dried with up to 50% w/w HSA, and more preferably with from 2 to 25% w/w HSA.

In view of the increased FPF and FPD obtained, especially when co-spray drying an active agent with an FCA, it may be possible to do away with the large carrier particles in a dry powder comprising an active agent which has been co-spray dried with a force control agent. However, it may still be desirable to include carrier particles, especially where the active agent is to be administered in small amounts, as the bulk of the larger carrier particles will help to ensure that an accurate dose is dispensed.

Alternative FCAs which could be co-spray dried with the heparin include phospholipids and lecithins. However, where the active agent is insoluble in organic solvents, whilst the FCA is insoluble in an aqueous phase, or vice versa, in order to co-spray dry these incompatible materials, one must use a technique such as hydrophobic ion pairing.

Alternative Droplet Formation

It has further been discovered that the FPF and FPD of the dry powder formulation is also affected by the means used to create the droplets which are spray dried. Different means of forming droplets can affect the size and size distribution of the droplets, as well as the velocity at which the droplets travel when formed and the gas flow around the droplets. In this regard, the velocity at which the droplets travel when formed and the gas (which is usually air) flow around the droplets can dramatically affect size, size distribution and shape of resulting dried particles.

According to a second aspect of the invention, a method of preparing a dry powder composition is provided, wherein the active agent is spray dried using a spray drier comprising a means for producing droplets moving at a controlled velocity and of a predetermined droplet size. The velocity of the droplets is preferably controlled relative to the body of gas into which they are sprayed. This can be achieved by

controlling the droplets' initial velocity and/or the velocity of the body of gas into which they are sprayed.

It is clearly desirable to be able to control the size of the droplet formed during the spray drying process and the droplet size will affect the size of the dried particle. Preferably, the droplet forming means also produces a relatively narrow droplet, and therefore particle, size distribution. This will lead to a dry powder formulation with a more uniform particle size and thus a more predictable and consistent FPF and FPD.

The ability to control the velocity of the droplet also allows further control over the properties of the resulting particles. In particular, the gas speed around the droplet will affect the speed with which the droplet dries. In the case of droplets which are moving quickly, such as those formed using a 2-fluid nozzle arrangement (spraying into air), the air around the droplet is constantly being replaced. As the solvent evaporates from the droplet, the moisture enters the air around the droplet. If this moist air is constantly replaced by fresh, dry air, the rate of evaporation will be increased. In contrast, if the droplet is moving through the air slowly, the air around the droplet will not be replaced and the high humidity around the droplet will slow the rate of drying. As discussed below in greater detail, the rate at which a droplet dries affects various properties of the particles formed, including FPF and FPD.

Preferably the velocity of droplets at 10 mm from their point of generation is less than 100 m/s, more preferably less than 50 m/s, most preferably less than 20 m/s. Preferably the velocity of the gas, used in the generation of the droplets, at 10 mm from the point at which they are generated is less than 100 m/s, more preferably less than 50 m/s, most preferably less than 20 m/s. In an embodiment, the velocity of the droplets relative to the body of gas into which they are sprayed, at10 mm from their point of generation, is less than 100 m/s, more preferably less than 50 m/s, most preferably less than 20 m/s.

Preferably, the means for producing droplets moving at a controlled velocity and of a predetermined size is an alternative to the commonly used 2-fluid nozzle. In one embodiment, an ultrasonic nebuliser (USN) is used to form the droplets in the spray drying process.

Whilst ultrasonic nebulisers (USNs) are known, these are conventionally used in inhaler devices, for the direct inhalation of solutions containing drug, and they have not previously been widely used in a spray drying apparatus. However, it has been discovered that the use of such a nebuliser in spray drying has a number of important advantages and these have not previously been recognised.

USNs use an ultrasonic transducer which is submerged in a liquid. The ultrasonic transducer (a piezoelectric crystal) vibrates at ultrasonic frequencies to produce the short wavelengths required for liquid atomisation. In one common form of USN, the base of the crystal is held such that the vibrations are transmitted from its surface to the nebuliser liquid, either directly or via a coupling liquid, which is usually water. When the ultrasonic vibrations are sufficiently intense, a fountain of liquid is formed at the surface of the liquid in the nebuliser chamber. Large droplets are ejected from the apex and a "fog" of small droplets is emitted. A schematic diagram showing how the USN works is shown in Figure 3.

The attractive characteristics of USNs for producing fine particle dry powders include: low spray velocity; the small amount of carrier gas required to operate the nebulisers; the small droplet size and narrow droplet size distribution produced; the simple nature of the USNs (the absence of moving parts which can wear, etc.); and the ability to accurately control the gas flow around the droplets, thereby controlling the rate of drying.

To elaborate, USNs do not separate the liquid into droplets by increasing the velocity of the liquid. Rather, the necessary energy is provided by the vibration caused by the ultrasonic nebuliser.

Thus, as an alternative to the conventional Büchi two-fluid nozzle, an ultrasonic nebuliser (Mini Humidifier) may be used to generate droplets of active agent, which are then dried within the Büchi drying chamber. In one arrangement, the USN is placed in the feed solution comprising an active agent in a specially designed glass chamber which allows introduction of the cloud of droplets generated by the USN directly into the heated drying chamber of the spray dryer.

The two-fluid nozzle is left in place to seal the hole in which it normally sits, but the compressed air was not turned on. The drying chamber is then heated up to 150°C inlet temperature, with 100% aspirator setting. Due to the negative pressure of the Büchi system, the nebulised cloud of droplets is easily drawn into the drying chamber, where the droplets are dried to form particles, which are subsequently classified by the cyclone, and collected in the collection jar. It is important that the level of feed solution in the chamber is regularly topped up to avoid over concentration of the feed solution as a result of continuous nebulisation.

In an embodiment of the present invention, the method of preparing the active particles involves the use of an ultrasonic nebuliser. Preferably, the ultrasonic nebuliser is incorporated in a spray drier.

Two theories have been developed which describe the mechanism of liquid disintegration and aerosol production in ultrasonic devices (Mercer 1981, 1968 and Sollner 1936). Lang (1962) observed that the mean droplet size generated from thin liquid layers was proportional to the capillary wavelength on the liquid surface. Using the experimentally determined factor of 0.34, the droplet diameter D is given by:

$$d_p = 0.34 \ (8\pi\gamma/pf^2)^{1/3}$$

p = solution density g cm^{-3} (water = 1)

γ = surface tension dyn cm^{-1} (water = 70)

f = frequency (MHz)

This means that for a frequency of 1.7 MHz the calculated droplet size is 2.9μm and for 2.4 MHz the calculated droplet size is 2.3 μm. Atomisers are also available with frequencies up to 4 MHz with a calculated droplet size of 1.6 μm.

Clearly, this allows the size of the droplets to be accurately and easily controlled, which in turn means that the active particle size can also be controlled (as the dried particle size will depend, to a great extent, on the size of the droplet).

Firstly, a USN was used to prepare dry powders using a feed solution of an active agent (heparin) alone, and a blend of active agent with 1% to 5% and 10% w/w FCA (l-leucine). The ultrasonic nebuliser feed flow rate was 130 ml/hr. The furnace temperature of the nebulised powders was set at 350°C. Figure 4 shows a schematic drawing of the ultrasonic set-up.

In order to test the processing of the powders, work was conducted using a Monohaler and a capsule filled with 20 mg powder and fired into a rapid TSI in the manner explained previously. The study used a TSI flow rate of 60lpm with a cut-off of approximately 5μm.

Three measurements were made for each blend and the results are summarised below in Table 10, giving the average values of the three sets of results obtained.

Table 10: rapid TSI results using the dry powder produced using a USN with varying amounts of FCA

Formulation	FPF% (metered dose)	FPD (mg)
Heparin (0% leucine)	1.1	0.22
Heparin + leucine (1% w/w)	17.4	3.5
Heparin + leucine (2% w/w)	30.2	6.0
Heparin + leucine (3% w/w)	28.6	5.7
Heparin + leucine (4% w/w)	48.4	9.7
Heparin + leucine (5% w/w)	41.5	8.3
Heparin + leucine (10% w/w)	55.8	11.8

The rapid TSI results using the dry powder produced using the USN indicate a low aerosolisation efficiency for pure heparin particles, but an improvement appeared in FPF with addition of l-leucine as a FCA.

The morphology of the particles was viewed using scanning electron micrographs (SEMs) prepared as set out above.

Figure 5a shows SEM micrographs of USN spray dried heparin alone (without secondary drying), whilst Figure 5b shows SEM micrographs of USN spray dried heparin with 10% leucine (without secondary drying).

As can be clearly seem from the SEMs, the shape of particles formed by co-spray drying an active agent and leucine using a USN differs to that of particles formed by co-spray drying heparin and leucine using a conventional 2-fluid nozzle spray drying technique.

The SEM micrographs of pure heparin generated using a USN show that the particles have a size of approximately 2μm or less. The SEMs also show that these particles tend to form "hard" agglomerates of up to 200μm.

In contrast, the SEMs of nebulised heparin and leucine show that the primary particles produced are of the same size as the pure heparin particles. However, these particles are discrete and agglomerates are not evident.

What is more, the distinctive dimples or wrinkles observed on the surface of the particles prepared by co-spray drying heparin and leucine using a 2-fluid nozzle spray drier (Figures 2a-2d) are not present when the particles are spray dried using a USN. Despite this, the co-spray dried particles formed using a USN still have an improved FPF and FPD over particles formed in the same way but without the FCA. In this case, this improvement is clearly not due to the shape of the particles.

We believe the leucine concentration at the surface of the solid particles is governed by several factors. These include the concentration of leucine in the solution which

forms the droplets, the relative solubility of leucine compared to heparin, the surface activity of leucine, the mass transport rate within the drying droplet and the speed at which the droplets dry. If drying is very rapid it is thought that the leucine content at the particle's surface will be lower than that for a slower drying rate. The leucine surface concentration is determined by the rate of leucine transport to the surface, and its precipitation rate, during the drying process.

As mentioned above, high gas flow rates around the droplets can accelerate drying and it is thought that, because the gas flow around droplets formed using a USN is low in comparison to that around droplets formed using conventional 2-fluid nozzles, droplets formed using the former technique dry more slowly than those produced by using conventional 2-fluid nozzles. The leucine (or other FCA) concentration on the shell of droplets and dried particles produced using a USN can be higher as a result. It is considered that these effects reduce the rate of solvent evaporation from the droplets and prevent "blowing" and, therefore, are responsible for the physically smaller and smoother primary particles we have observed (Kodas, T.T and Hampden Smith, M., 1999, Aerosol Processing of materials,440). In this last regard, and as previously noted, droplets formed by the 2-fluid nozzle system have rapid air flow around them and they, therefore, dry very rapidly, and suffer from the effects of blowing.

In a particle size study, the particle size of the spray dried particles formed using the USN was analysed. The dry powders were dispersed at 4bar in a Helos disperser. The values of FPF <5μm and D10, D50 and D90 of the ultrasonic nebulised powders were measured and are indicated in Table 11 (10% by volume of the particles are of a size, measured by Malvern, that is below the D10 value. 50% by volume of the particles are of a size, measured by Malvern, that is below the D50 value and so on). The values are an average of three measurements.

Table 11: Particle size study of spray dried particles using USN, without secondary drying

Formulation	D10 (μm)	D50 (μm)	D90 (μm)	FPF% (<5μm)
Heparin (0% leucine)	0.43	1.07	4.08	90.52
Heparin + leucine (1% w/w)	0.41	0.90	1.79	99.97
Heparin + leucine (2% w/w)	0.41	0.89	1.75	100
Heparin + leucine (3% w/w)	0.41	0.88	1.71	100
Heparin + leucine (4% w/w)	0.41	0.86	1.71	100
Heparin + leucine (5% w/w)	0.41	0.90	1.84	100
Heparin + leucine (10% w/w)	0.41	0.89	1.76	100

Figure 6 shows a typical size distribution curve of three repeated tests of pure heparin powder generated using an ultrasonic nebuliser. The main peak represents the size of the individual active particles, ranging between 0.2μm and 4.5μm in diameter. The second, smaller peak between diameters of 17 to 35μm represents agglomerates of active particles.

Sympatec particle sizing (Helos dry dispersed) results showed that ultrasonic nebulised powders have a narrower size distribution and smaller mean particle size than the 2-fluid nozzle spray dried powders.

Figure 7a shows a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin with 2% leucine w/w.

Figure 7b shows a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin with 5% leucine w/w.

Figure 7c shows a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin with 10% leucine w/w.

These figures show a gradual disappearance of the second peak, indicating that the incidence of agglomerates is reduced as the amount of co-spray dried FCA is increased.

For the USN, spray dried material, agglomerate peaks disappears under the same test conditions when > 3 % leucine is added. For the 2-fluid nozzle spray dried material, agglomerate peaks disappear under the same test conditions when >10% leucine is added. This indicates that adding leucine as an FCA reduces the strength of the agglomerates in heparin powder. It further suggests that ultrasonic nebulised materials de-agglomerate more easily at lower leucine (FCA) contents. This may be related to the surface concentration of the leucine (FCA), as mentioned above.

The SEM images of ultrasonic nebulised powders (Figures 5a and b) also support the finding that addition of leucine facilitates aerosolisation. SEMs of pure heparin showed that although heparin primary particles are <2μm, large distinct agglomerates are formed. The SEMs of all of the powders comprising heparin and leucine show that the primary particle size is still <2μm, but the large agglomerates are not evident.

It can be seen that particles formed using a spray drying process involving an ultrasonic nebuliser have been found to have a greater FPF than those produced using a standard spray drying apparatus, for example with a two nozzle configuration.

What is more, the particles formed using a spray drying process using a USN have been found to have a narrower particle size distribution than those produced using a standard spray drying apparatus, for example with a two nozzle configuration.

Similar results to those shown above when using USNs are expected for spray drying using other means which produce low velocity droplets. For example, further alternative nozzles may be used, such as electrospray nozzles or vibrating orifice nozzles. These nozzles, like the ultrasonic nozzles, are momentum free, resulting in a spray which can be easily directed by a carrier air stream.

Another attractive type of nozzle for use in a spray drying process is one which utilises electro-hydrodynamic atomisation. A tailor cone is created at a fine needle by applying high voltage at the tip. This shatters the droplets into an acceptable monodispersion. This method does not use a gas flow, except to transport the droplets after drying. An acceptable monodispersion can also be obtained utilising a spinning disc generator.

The nozzles such as ultrasonic nozzles, electrospray nozzles or vibrating orifice nozzles can be arranged in a multi nozzle array, in which many single nozzle orifices are arranged in a small area and facilitate a high total throughput of feed solution. The ultrasonic nozzle is an ultrasonic transducer (a piezoelectric crystal). If the ultrasonic transducer is located in an elongate vessel the output may be raised significantly.

Moisture Profiling

When active particles are produced by spray drying, some moisture will remain in the particles. This is especially the case where the active agent is temperature sensitive and does not tolerate high temperatures for the extended period of time which would normally be required to remove further moisture from the particles.

The amount of moisture in the particles will affect various particle characteristics, such as density, porosity, flight characteristics, and the like.

Therefore, according to a third aspect of the present invention, a method of preparing a dry powder composition is provided, wherein the method comprises a step of adjusting the moisture content of the particles.

In one embodiment, the moisture adjustment or profiling step involves the removal of moisture. Such a secondary drying step preferably involves freeze-drying, wherein the additional moisture is removed by sublimation. An alternative type of drying for this purpose is vacuum drying.

Generally, the secondary drying takes place after the active has been co-spray dried with a force control agent. In another embodiment, the secondary drying takes place after nebulised active agent has been spray dried, wherein the active agent was optionally in a blend with a FCA.

The secondary drying step has two particular advantages. Firstly, it can be selected so as to avoid exposing the pharmaceutically active agent to high temperatures for prolonged periods. Furthermore, removal of the residual moisture by secondary drying is significantly cheaper than removing all of the moisture from the particle by spray-drying. Thus, a combination of spray drying and freeze-drying or vacuum drying is economical and efficient, and is suitable for temperature sensitive pharmaceutically active agents.

In order to establish the effect of secondary drying of the powders, samples of active agent alone and of a combination of active agent (heparin) and an FCA (leucine 10% w/w), were secondary dried at 50°C under vacuum for 24 hours.

The results set out in Table 12 indicate the secondary drying step further raised the FPF and FPD, when they are compared to the results in Table 10, which relates to equivalent particles which have not undergone secondary drying.

Table 12: rapid TSI results using the dry powder produced using a USN with varying amounts of FCA, after secondary drying

Formulation	FPF% (metered dose)	FPD (mg)
Heparin (0% leucine)	4.1	0.82
Heparin + leucine (10% w/w)	70.8	14.2

In a later stage experiments have been conducted on samples of active agent (heparin) and an FCA (leucine 5% w/w), were secondary dried at 40°C under vacuum for 24 hours.

Particle size tests were also conducted to show the effect of secondary drying. The particle size of the spray dried particles formed using the USN was analysed. The dry powders were dispersed at 4bar in a Helos disperser. The powders were secondary dried over 24 hours under vacuum.

The values of FPF <5μm and D10, D50 and D90 of the ultrasonic nebulised powders were measured and are indicated in Table 14.

Table 14: Particle size study of spray dried particles using USN, after secondary drying

Formulation	D10	D50	D90	FPF% (<5μm)
Heparin (0% leucine)	0.44	1.06	2.93	92.35
Heparin + leucine (10% w/w)	0.40	0.87	1.77	100

Thus, by comparing the results in Table 14 with those of Table 11, one can see that secondary drying particles did not result in any significant change in particle size, both for active agent alone and for a blend of active agent and FCA.

Figure 8 shows a comparison between particle size distribution curves of secondary dried and not secondary dried powders. The powder used was heparin with 10% leucine w/w. Clearly, there is virtually no difference between the curves, illustrating that secondary drying does not have an effect on particle size.

Then, in order to establish whether the effect of secondary drying varied between particles produced using a USN and a 2-fluid nozzle, the particle size study of secondary drying with spray dried particles formed using the USN was repeated but using a 2-fluid nozzle spray drier. Once again, the powders were secondary dried over 24 hours under vacuum. Values of FPF <5μm and D10, D50 and D90 of the spray dried powders are indicated in Table 15 below.

Table 15: Particle size study of 2-fluid nozzle spray dried particles after secondary drying

Formulation	D10	D50	D90	FPF% (<5μm)
Heparin + leucine (2% w/w)	0.59	2.09	5.19	89.57
Heparin + leucine (5% w/w)	0.61	2.16	4.77	91.18
Heparin + leucine (10% w/w)	0.58	2.04	3.93	96.6
Heparin + leucine (25% w/w)	0.63	2.34	4.85	91.15
Heparin + leucine (50% w/w)	1.05	3.03	6.62	80.03

Figures 2e to 2h show SEM micrographs of 2-fluid nozzle spray dried heparin with 2, 5, 10 and 50% leucine, after secondary drying. When one compares the particles in these Figures to those in Figures 2a-d, it can be seen that the secondary drying does appear to increase the "collapse" of the particles. Thus, even at low percentages of FCA, the secondary dried particles have a more wrinkled or shrivelled shape.

Table 16: Moisture content of 2 fliud nozzle spray dried particles under standard condition

Formulation	% w/w Moisture before secondary drying	% w/w Moisture after secondary drying
Heparin + Leucine 5%	9.57	2.18

The above discussed experiments and the moisture content values determined by Karl-Fisher methodology set out in Table 16 show that secondary drying significantly reduces the moisture content of heparin particles (by approximately 6.5 %). This would imply that the heparin is drying in such a way that there is a hard outer shell holding residual moisture, which is driven off by secondary drying, and entrapped moisture is trapped with in a central core. One could infer that the residence time of the particle in the drying chamber is too short, and that the outer shell is being formed rapidly and is too hard to permit moisture to readily escape during the initial spray drying process.

Secondary drying can also be beneficial to the stability of the product, by bringing down the moisture content of a powder. It also means that drugs which may be very heat sensitive can be spray dried at lower temperatures to protect them, and then subjected to secondary drying to reduce the moisture further, and protect the drug.

In another embodiment of the third aspect of the invention, the moisture profiling involves increasing the moisture content of the spray dried particles.

Preferably, the moisture is added by exposing the particles to a humid atmosphere. The amount of moisture added can be controlled by varying the humidity and/or the length of time for which the particles are exposed to this humidity.

From the results presented herein, it can be seen that improvement in the FPF of spray dried active agents can be achieved by using one or more of the following:

1) co-spray drying the active agent with a force control agent;
2) using a means of producing droplets for spray drying which results in slow velocity droplets, the size of which can be accurately controlled; and
3) moisture profiling of the spray dried particles.

The above discussion and experiments focussed on conventional spray drying apparatus and ultrasonic nebulizing apparatus. However, it should be noted that further changes to the apparatus may be made to ensure that the particles collected at the end of the spray drying process have the optimum properties.

For example, the nature of the drying chamber may be changed, to get better drying and/or other advantages. Thus, in one embodiment of the invention, a spray drying apparatus comprising a drying chamber with heated walls may be used. Such drying chambers are known and they have the advantage that the hot walls discourage deposition of the spray dried material on them. However, the heated walls create a temperature gradient within the drying chamber, where the air in the outer area of the chamber is hotter than that in the centre of the chamber. This uneven temperature can cause problems because particles which pass through different

parts of the drying chamber will have slightly different properties as they may well dry to differing extents.

In an alternative embodiment, the spray drying apparatus comprises a radiative heat source in the drying chamber. Such heat sources are not currently used in spray drying. This type of heat source has the advantage that it does not waste energy heating the air in the drying chamber. Rather, only the droplets/particles are heated as they pass through the chamber. This type of heating is more even, avoiding the temperature gradients mentioned above in connection with drying chambers with heated walls. This also allows the particles to dry from inside the droplets thus reducing or avoiding crust forming.

In yet another embodiment, the spray dried particles are collected using a vertical drying column. These columns are already known in spray drying devices and they collect the spray dried particles by carrying the particles up a vertical column using an air flow, rather than simply relying on gravity to collect the particles in a collection chamber. The advantage of using such a vertical drying column to collect the spray dried particles is that it allows for aerodynamic classification of the particles. Fine particles tend to be carried well by the air flow, whilst larger particles are not. Therefore, the vertical drying column does not collect these larger particles.

Claims

1. A method of making a dry powder composition for pulmonary inhalation, the method comprising spray drying a pharmaceutically active agent to produce active particles, wherein the active agent is co-spray dried with a force control agent.

2. A method as claimed in claim 1, wherein the force control agent is an amino acid, a phospholipid or a metal stearate.

3. A method as claimed in claim 2, wherein the force control agent is one or more of leucine, lysine and cysteine.

4. A method as claimed in any one of the preceding claims, wherein the active agent is a small molecule.

5. A method as claimed in any one of claims 1-3, wherein the active agent is not a macromolecule.

6. A method as claimed in any one of the preceding claims, wherein a blend of active agent and force control agent is spray dried, and the blend is a solution.

7. A method as claimed in any one of claims 1-5, wherein a blend of active agent and force control agent is spray dried, and the blend is a suspension.

8. A method as claimed in any one of the preceding claims, wherein a solid content of up to 5% w/w active agent is spray dried.

9. A method as claimed in any one of the preceding claims, wherein the active agent is co-spray dried with 1-50% w/w force control agent.

10. A method as claimed in claim 9, wherein the active agent is co-spray dried with less than 10% w/w force control agent, preferably less than 5% w/w.

11. A method as claimed in any one of the preceding claims, wherein the active agent is spray dried using a spray drier comprising a 2-fluid nozzle.

12. A method as claimed in any one of claims 1-10, wherein the active agent is spray dried using a spray drier comprising a means for producing droplets moving at a controlled velocity and of a predetermined size.

13. A method as claimed in claim 12, wherein the spray drier comprises an ultrasonic nebuliser.

14. A method as claimed in any one of the preceding claims, wherein the method comprises adjusting the moisture content of the spray dried particles.

15. A method as claimed in claim 14, wherein adjusting the moisture content involves a secondary drying step.

16. A method as claimed in claim 14, wherein the secondary drying step involves drying the spray dried particles under a vacuum or freeze-drying the particles.

17. A method as claimed in claim 14, wherein adjusting the moisture content involves increasing the moisture content of the particles.

18. A dry powder composition for pulmonary inhalation, wherein the composition comprises particles of pharmaceutically active material prepared using a method as claimed in any one of the preceding claims.

Abstract

Pharmaceutical Compositions

The present invention relates to improvements in dry powder formulations comprising a pharmaceutically active agent for administration by inhalation, and in particular to methods of preparing dry powder compositions with improved properties. In particular, spray drying processes are adapted and adjusted to obtain active particles with higher fine particle fractions and fine particle doses.

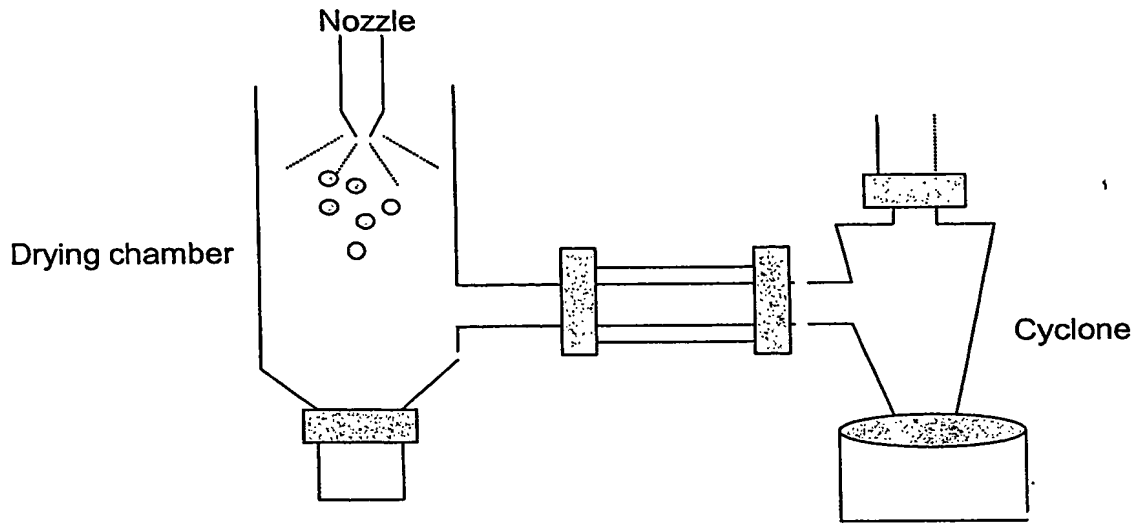


Figure 1

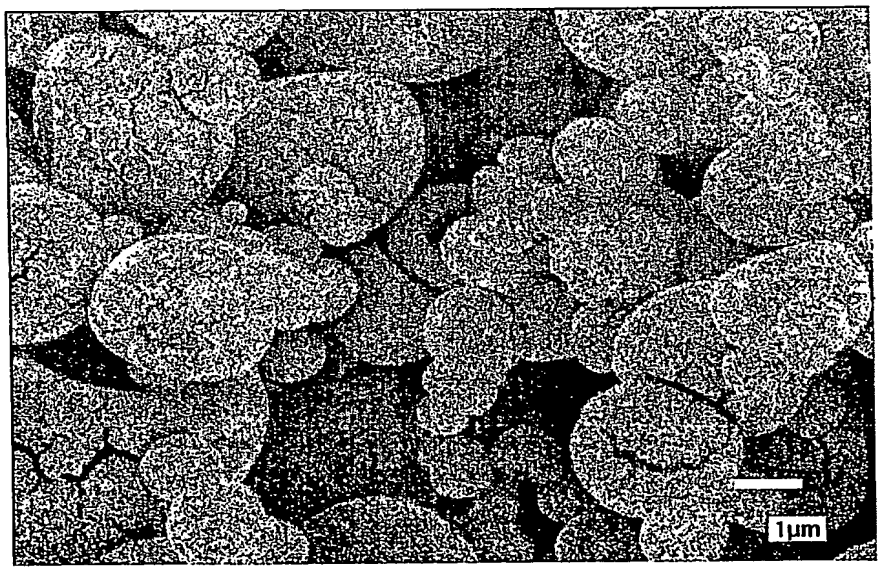


Figure 2a

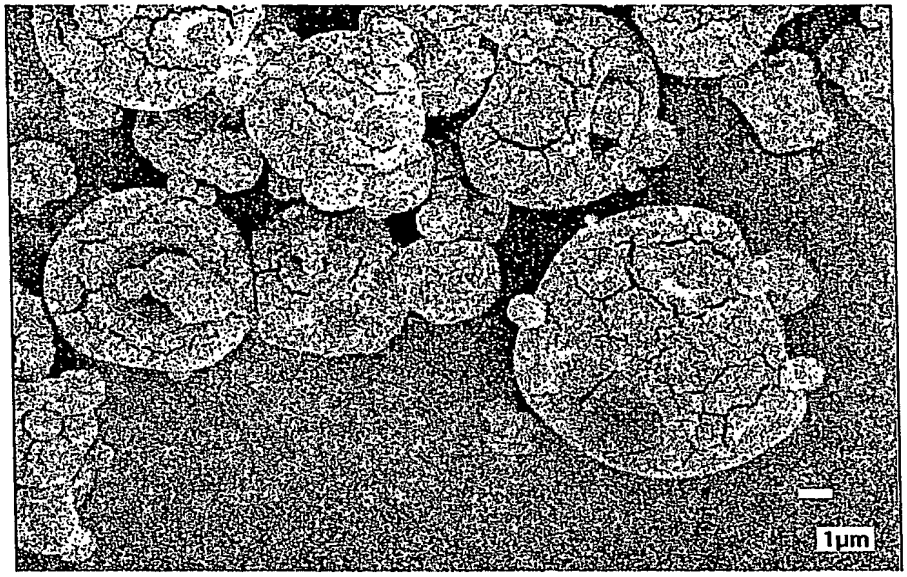


Figure 2b

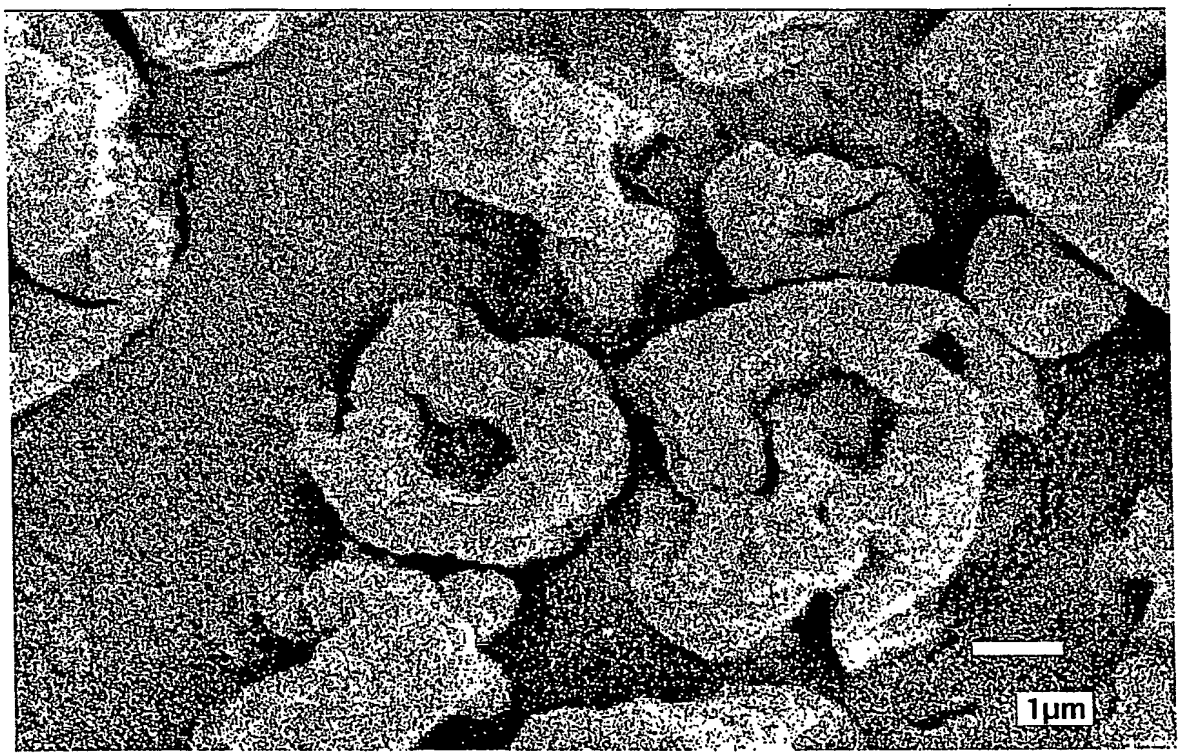


Figure 2c

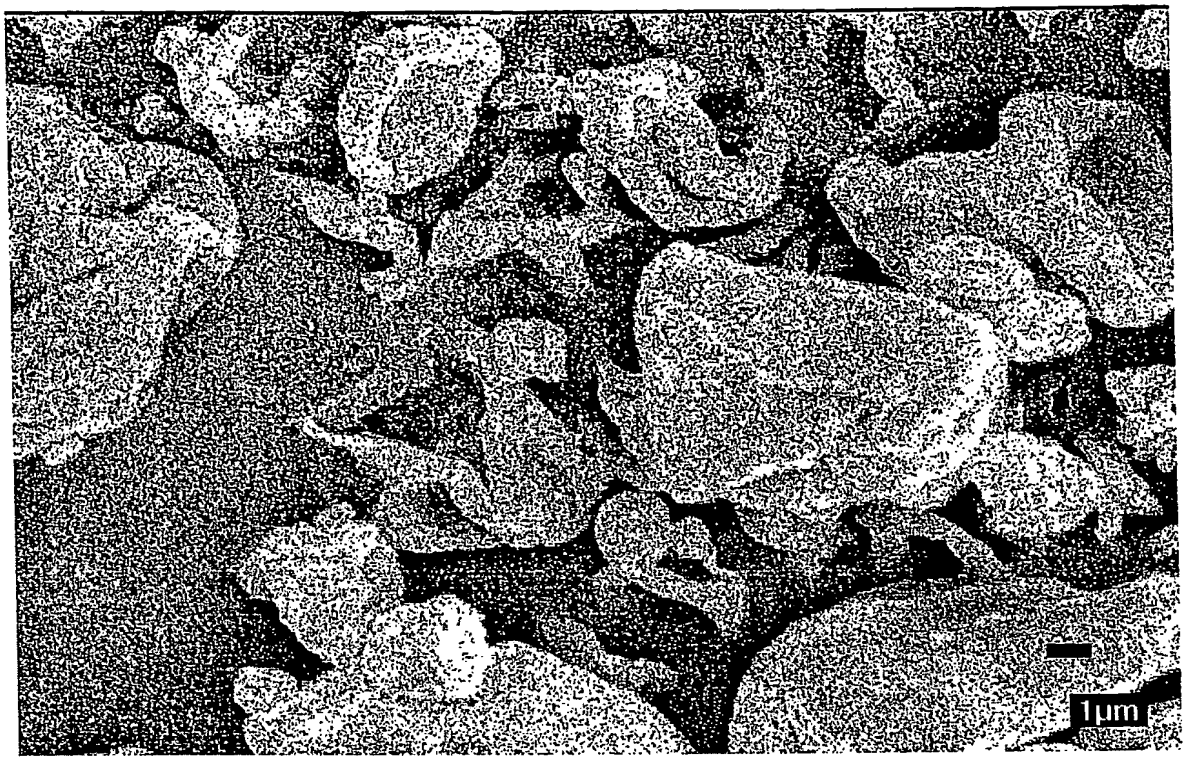


Figure 2d

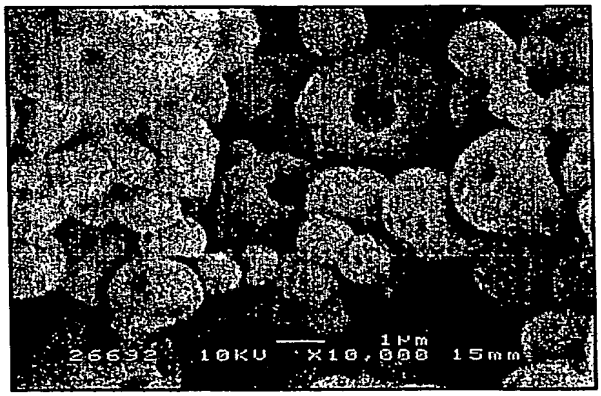


Figure 2e

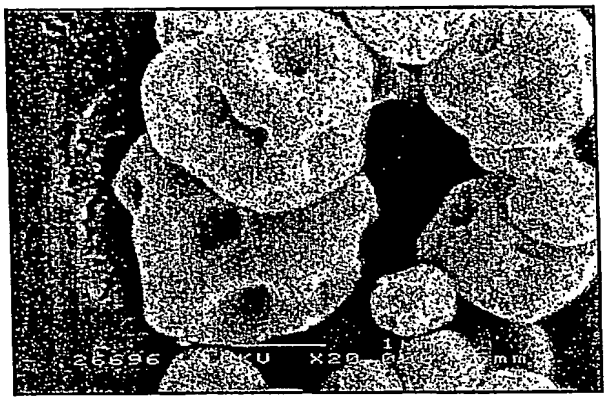


Figure 2f

Figure 2g

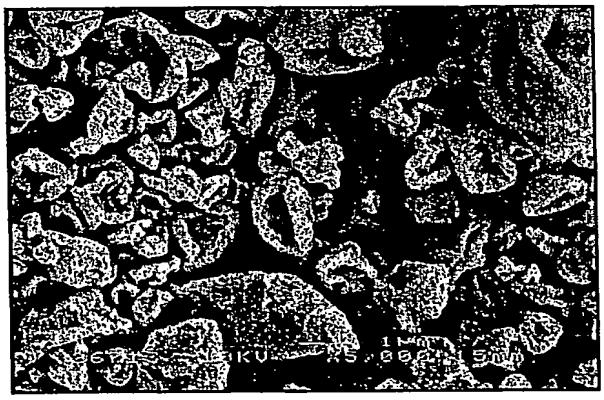


Figure 2h

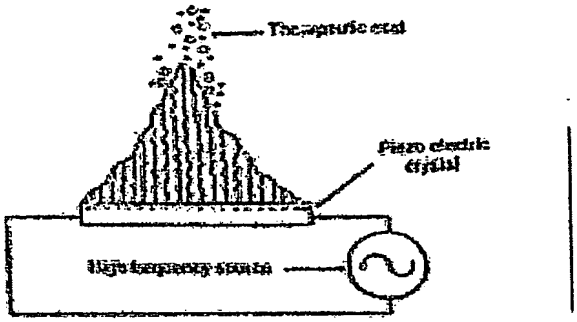
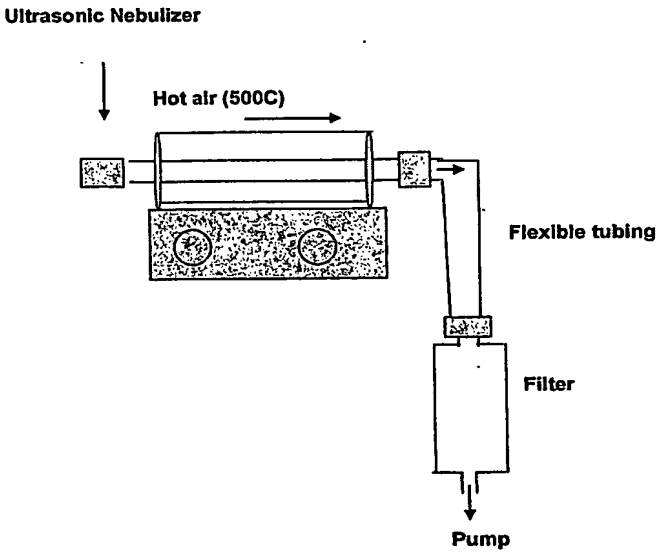


Figure 3



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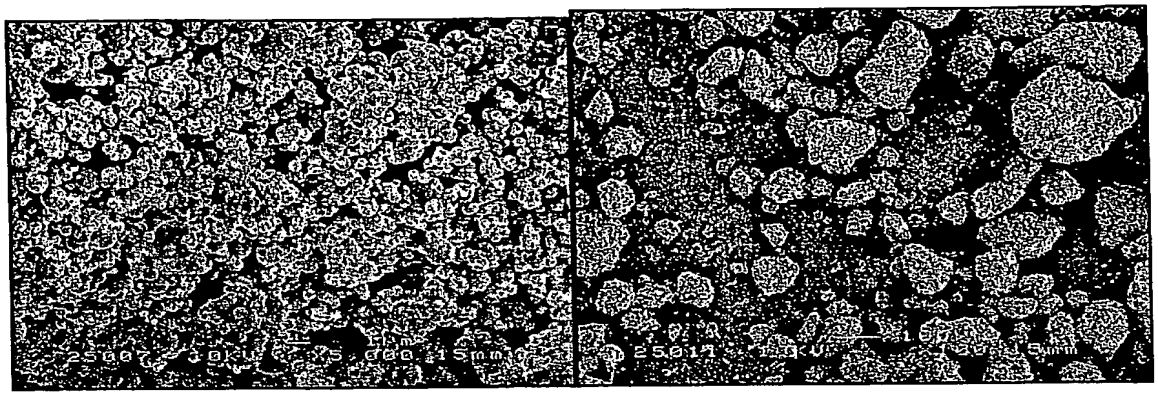

Figure 5a

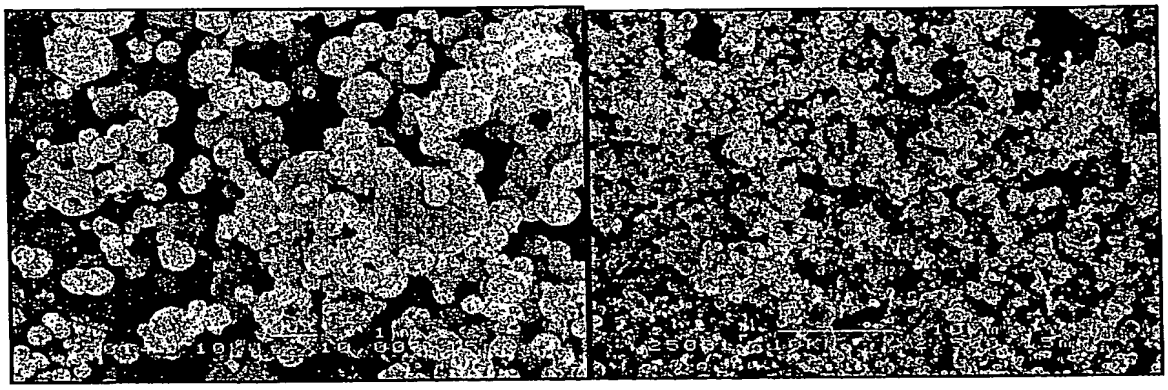

Figure 5b

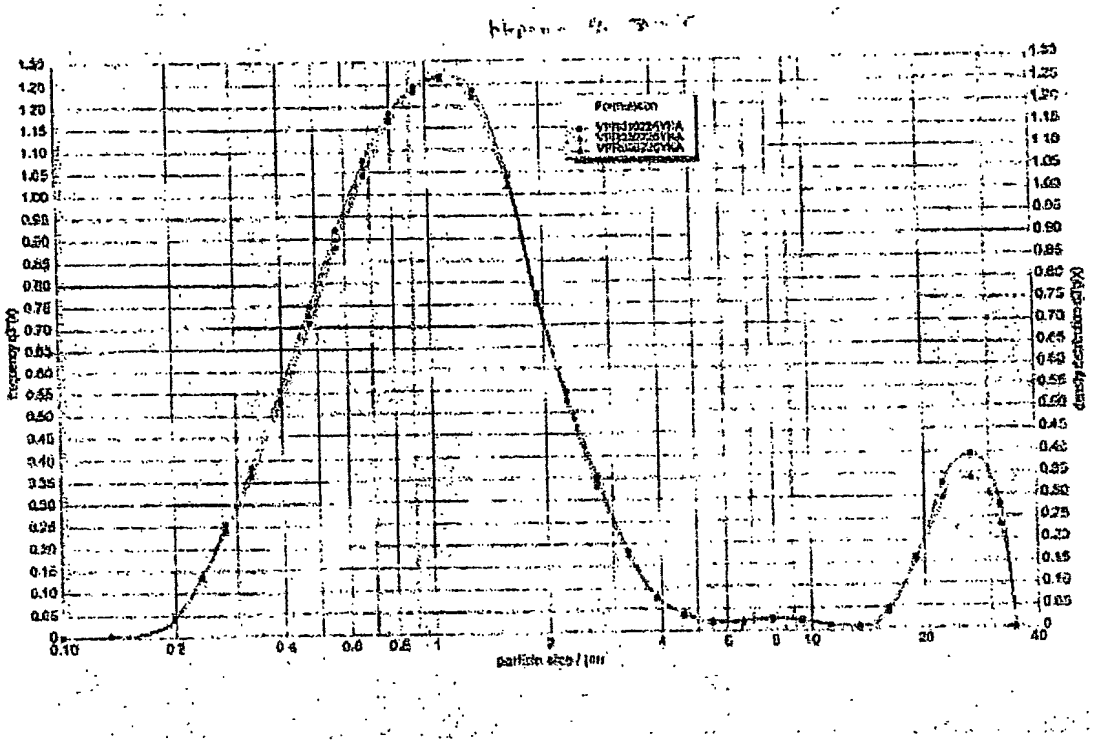

Figure 6

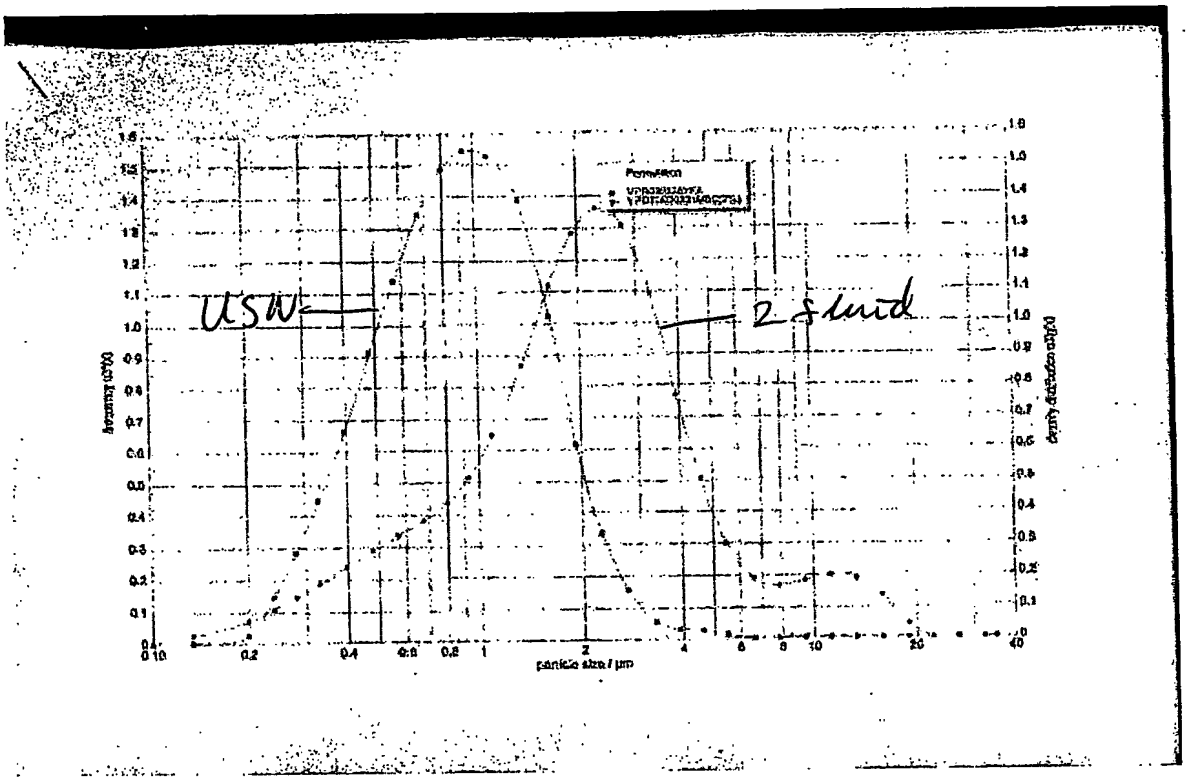

Figure 7a

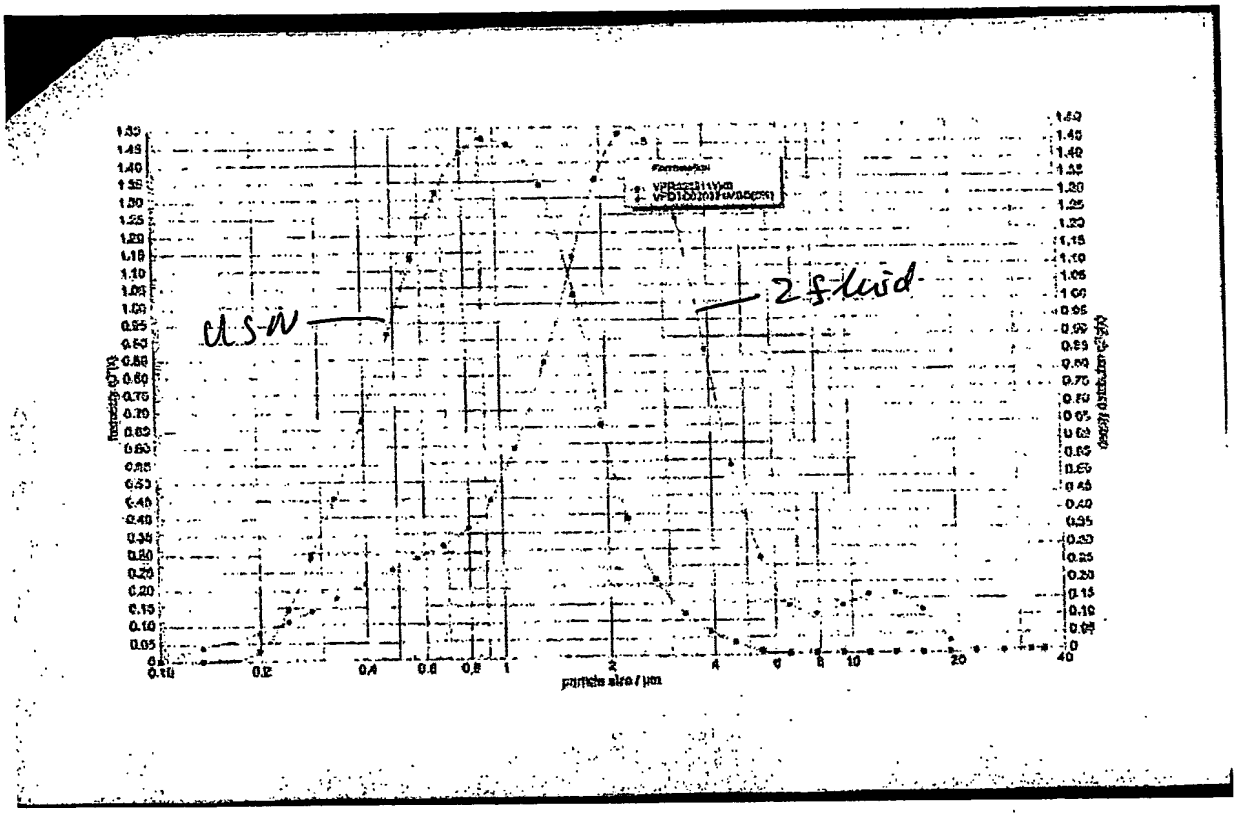

Figure 7b

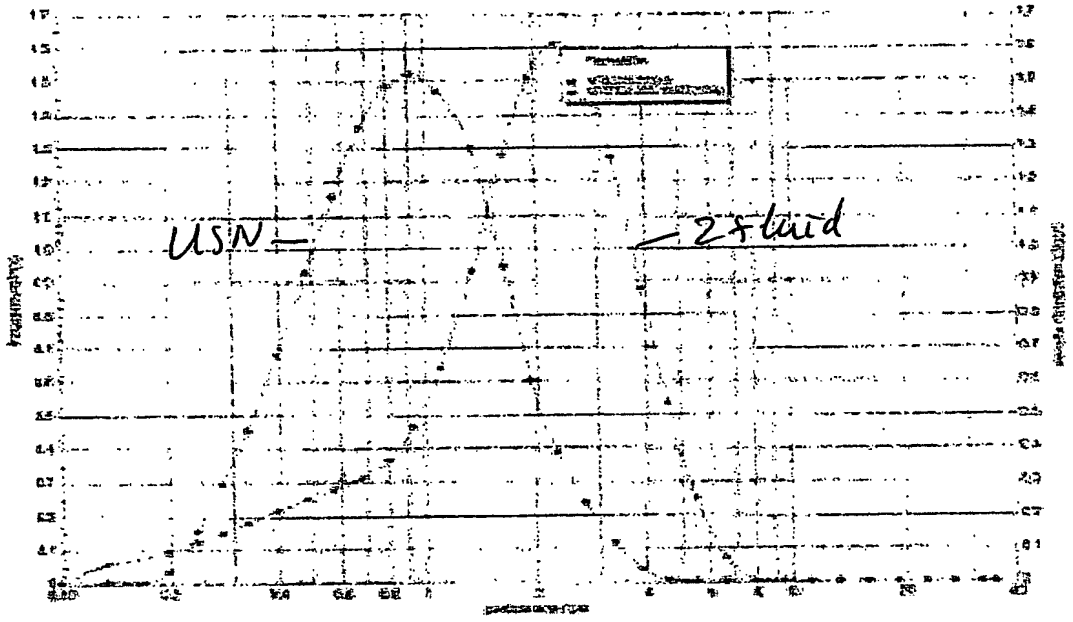

Figure 7c

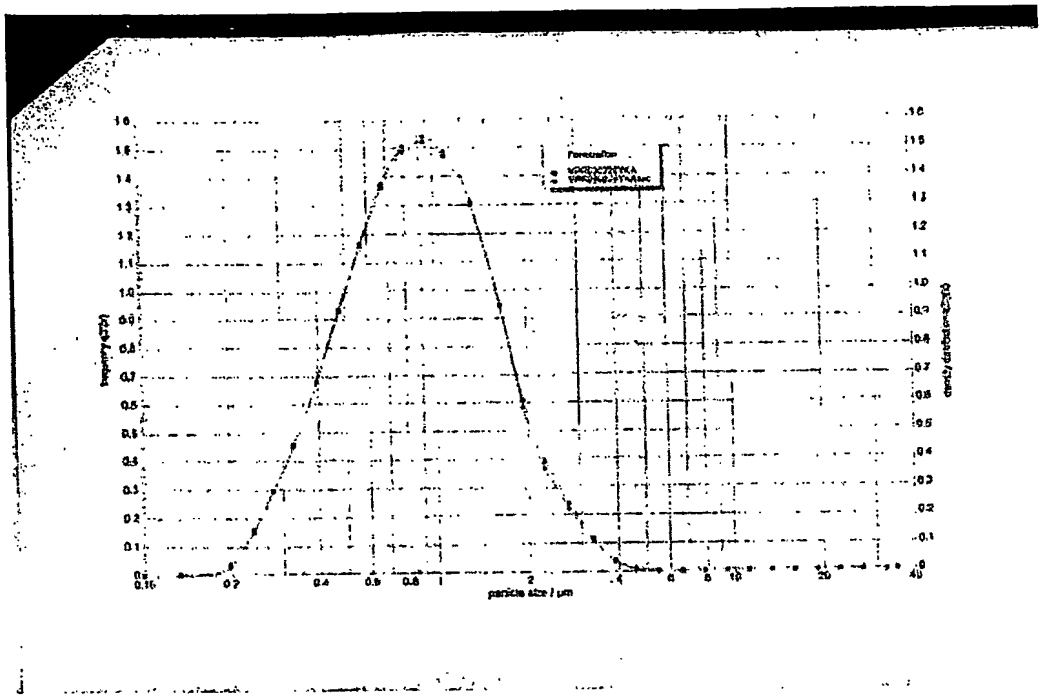

Figure 8